REMARKS

Rejections under 35 U.S.C. 112, first paragraph

The Office Action maintains the rejection of claims 221-225, 231 and 233-263 because the claims allegedly are not sufficiently enabled throughout their scope. In particular, the Office Action maintains that the specification does not adequately enable nuclear transfer in which the donor genetic material is not contained in a donor nucleus. While they respectfully disagree with the Office's position, Applicants have deleted the offending subject matter out of a spirit of cooperation in an effort to have the case more promptly allowed.

Rejections of claims under 35 U.S.C. 103

The Office Action also maintains the obviousness rejection over various references. The cited references teach (1) the use of somatic cells in nuclear transfer (Stice and Campbell), (2) the use of polymerase inhibitors to arrest blastomere donor cells in nuclear transfer processes (Collas), and (3) the use CDK2 kinase inhibitors as chemotherapeutic agents (Alessi). None of the references teach the use of a ***CDK2 kinase inhibitor*** to arrest a ***somatic*** donor cell in G1 before performing nuclear transfer, as recited in the pending claims.

A. The cited references do not support a prima facie case of obviousness.

Before Applicants made their claimed invention, there were two schools of thought on cloning animals from somatic cells. The first school of thought was adopted by researchers at the Roslin Institute and reported in Cambell's US 6,147,276. These researchers were the first to clone an animal from a somatic cell, and attributed their success to the use of quiescent donor cells. According to these researchers, it was necessary to induce quiescence in donor cells because quiescent nuclear material could be reprogrammed upon transfer to an enucleated oocyte so that it could once again support differentiation of dividing cells. They stated that "the fact that the G0 state is associated with cell differentiation suggests that this may provide a nuclear/chromatin structure which is more amenable to either remodeling and/or reprogramming by the recipient cell cytoplasm." (Col. 4, lines 62-66). In conclusion, they stated unequivocally that "to be useful in this invention, donor cells are [i.e. must be] quiescent, which is to say that they are not actively proliferating by means of the mitotic cell cycle." (Col. 4, lines 18-20).

The second school of thought, which was contemporaneously adopted by researchers at the University of Massachusetts and reported in Stice et al. (US 5,945,577), held that donor cells must be actively dividing in order to support reprogramming of the donor genetic material during the nuclear transfer process. Indeed, we understand that the Office took the position during the prosecution of the '577 patent that the "secret to successful cloning" lies in "reprogramming and activation of the embryos so that cell division occurs to the end of a cloned animal." Thus, the claims of Stice et al's '577 patent limit the invention expressly to "using as the donor cell or donor cell nucleus a ***proliferating*** somatic cell that has been expanded in culture, or a nucleus isolated from said somatic cell." (Claim 1). We understand that the Office required this limitation to be inserted into the claims based upon representations in the popular press (in particular USA Today) that the inventors had used "rapidly dividing cells" to support live birth of a cloned animal.

The claimed invention challenges both of these conventional schools of thought by employing somatic donor cells in an arrested state. Collas is the only reference that discloses the use of arrested cells in nuclear transfer. However, this reference is woefully insufficient because Collas employed arrested blastomeres. Moreover, even though Collas' studies were published over a decade ago, and Collas has worked with aphidicolin since his 1992 publication, he has never been able to produce a live offspring using aphidicolin in blastomeric or somatic cells, and has never reported such a success. Aphidicolin does not work to produce live offspring, and workers in this art area know it.

The present invention deviates even further from the prior art by employing CDK2 inhibitors to induce the arrested state. Alessi is cited to show that CDK2 inhibitors were known G1-arrest agents before the present invention. However, Alessi explored the use of CDK2 inhibitors as chemotherapeutic agents, and his teachings thus have no bearing on what a skilled worker would have done to produce live animals from nuclear transfer procedures.

To support a prima facie case of obviousness, the cited references must ***suggest*** the claimed combination. The references cited in the office action do not support a prima facie case of obviousness because there is no suggestion in Stice's or Campbell's earlier work to employ

donor cells arrested in G1 for the donor nuclear material. There also is no suggestion to use CDK2 kinase inhibitors to induce such arrest.

Moreover, there is no ***expectation of success***. The Office Action cites Collas to show an expectation of success from using G1 arrested cells in somatic cell nuclear transfer processes. However, Collas employed blastomeres as the donor cells. If Collas had suggested the utility of arresting somatic cells in G1 during the nuclear transfer process, then one certainly would have expected Campbell or Stice (two of the biggest pioneers in this field) to make such a disclosure in their original publications. Instead, Campbell and Stice specifically taught away from the use of G1 arrested donor cells by teaching the necessity of using either quiescent or actively dividing cells in the nuclear transfer process.

The fact of the matter is that skilled workers have not traditionally believed that teachings from the "blastomere" art can be readily applied to the science of somatic cell nuclear transfer, because of the need to reprogram somatic cells to allow cellular differentiation during the division process. Differences between blastomeres and somatic cells abound, such as the length of the G1 phase in proportion to the S, G2 and M phases, that suggest the need for reprogramming of the nucleus in the donor cell, and that teach away from the interconversion of teachings between the two fields. Campbell acknowledged these distinctions when, in the '276 patent, he states that "by virtue of the nuclear donor cells being in the quiescent state, the chromatin of the nuclei of the donors may be modified before embryo reconstitution or reconstruction such that the nuclei are able to direct development." (Col. 4, line 66 - col. 5, line 3). The Patent Office acknowledged these distinctions when, during the examination of Stice's '577 patent, the Examiner stated that the "secret to successful cloning" lies in "reprogramming and activation of the embryos so that cell division occurs to the end of a cloned animal." For these reasons, a skilled worker would not have expected to successfully perform somatic cell nuclear transfer using arrested somatic cells based upon the teachings of Collas.

Collas also would not have conferred an expectation of success because Collas employed aphidicolin and the present claims are limited to CDK2 kinase inhibitors. Aphidicolin is a DNA polymerase inhibitor that halts the cell cycle at the border between the G1 and S phases. In

contrast, the claimed CDK2 kinase inhibitors work upstream of DNA polymerases, and actually recruit DNA polymerases after forming a complex with cyclin.

Some historical perspective also is in order. Collas has never reported the production of live offspring using aphidicolin, using blastomeres or somatic cells as the donor cells. Aphidicolin does not work to produce live offspring, and workers in this art area know it. Collas himself expressed doubt about whether aphidicolin could produce live offspring when he states unequivocally "However, the extent of development in vivo of G1 transplants remains to be determined." For this reason as well, workers of ordinary skill would not have a reasonable expectation that one could perform nuclear transfer successfully using aphdicolin arrested cells.

The Office Action cites Alessi to show that CDK2 kinase inhibitors could be substituted for aphdicolin. However, Alessi investigated CDK2 kinase inhibitors because "such a class of molecules may represent a novel tool for inhibition of tumor cell growth," i.e. to kill cells. In addition, Alessi states unequivocally that "the identity of the protein substrates of these kinases is far from being completely discovered." (Alessi, p. 8, col. 2). Alessi investigated CDK2 kinase inhibitors as broad spectrum chemotherapeutic agents, and confers no expectation that the skilled worker could successfully use CDK2 kinase inhibitors in Collas' blastomere nuclear transfer process. Alessi certainly confers no expectation that CDK2 inhibitors could successfully be used in a somatic cell nuclear transfer process.

Therefore, the cited references fail to support a prima facie case of obviousness.

B. Unexpected superior results rebut any prima facie case of obviousness.

In addition, Applicants have presented unexpected superior results in example 7 that rebut any prima facie case of obviousness that could be stated. Example 7 compares the efficiency of nuclear transfer using donor cells arrested in G1 by 15 uM roscovitine versus donor cells induced to quiescence by serum starvation. Thus, example 7 presents a direct head-to-head comparison of the cloning efficiencies achieved in the present invention versus the cloning efficiencies achieved using the serum starvation method described in Campbell (1996). All of the experiments used bovine granulosa cells as the donor cells and bovine immature oocytes that had been matured and enucleated by methods described in Cibelli et al. (1998) as the recipient oocytes. Fusion of the donor nucleus and the recipient oocyte were performed as described in

Miyoshi et al. (2000), and the resulting NT unit was activated substantially as described in Goto et al. (1999). The embryos were then transferred to synchronous recipient female cows and the development of the embryos was monitored.

Table 1 below presents the results from the experiments.

TABLE 1

	% of live embryos past 200 days	Number of live births
Roscovitine treated donor cells	12.5 ± 2.0%	2
Serum starved donor cells	3.4 ± 1.7%	0

The number of oocytes from the roscovitine group to reach 200 days, and the number of live births from the roscovitine group, were substantially greater than the numbers achieved from the serum starved group, and could not have been expected from the prior art. These unexpected superior results rebut any prima facie case of obviousness that could be made against the pending claims.

What perhaps makes these results even more surprising is data presented in the specification showing that roscovotine treatment of donor cells results in a lower rate of development to the blastocyst stage than serum starvation. Example 6 states on page 39, lines 9-12 of the specification, that at day seven, only 12.9% of the roscovitine derived embryos had reached blastocyst stage, whereas 20.1% of the serum starved derived embryos had reached blastocyst. This slower development rate is surprising because it could not have been predicted from Collas' teachings. Also surprising is the fact that more live offspring were produced from roscovitine derived embryos despite this slower developmental rate.

These unexpected superior results over the prior art further prove the nonobviousness of the present invention.

CONCLUSION

It is believed that this application is in condition for allowance and an early notice of allowance is respectfully requested. If the examiner has any questions about the pending claims

or the arguments presented herein, she is invited to contact the undersigned at 404-572-3513. The Commissioner is authorized to charge any additional fee or credit any overpayment associated with this submission, to Deposit Account No. 11-0980.

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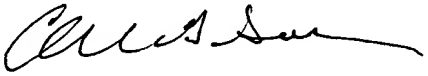

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